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Disease-a-Month

The Purpuras

WILLIAM J. HARRINGTON

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The Purpuras

WILLIAM J. HARRINGTON

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PURPURA is a term which may be applied to any cutaneous manifestation characterized by the intradermal or subdermal extravasation of blood. It is a physical sign featured in a variety of unrelated illnesses, the ultimate reflection of a number of derangements of hemostasis.

As an objective finding which most often connotes serious disease, purpura has excited comment since the earliest annals of medicine. Yet it is difficult for physicians to maintain up-to-date concepts of the mechanisms of hemostasis. Two reasons are foremost. On the one hand, only general physiologic principles relating to normal hemostasis are presently understood. In addition, identical factors have been unavoidably garbed in effective disguises by different investigators and thereby permitted several aliases. Few clinicians have either the time or the opportunity to assemble the acceptable data and construct a useful schema for the rational approach to differential diagnosis and management of the purpuric patient.

The following discussion will be devoted to an attempt to supply the important and clinically most useful information concerning each cause of purpura. But, since space is limited, an elaborate analysis of all physiologic observations is neither

desirable nor possible; indeed, for purposes of clarity, oversimplification will at times be necessary.

Three major topics will be considered: (1) normal hemostatic mechanisms, (2) clinical syndromes secondary to disturbances in hemostasis and (3) therapy. Less emphasis will be given to those forms of purpura due to abnormalities of blood coagulation, a complex etiologic category often considered separately, and primarily dermatologic disorders will not be discussed.

NORMAL HEMOSTATIC MECHANISMS

The anatomy of hemostasis may be conveniently divided into three parts: the extravascular, the vascular and the intravascular components. The first is concerned primarily with the structural support of blood vessels, the second with their integrity and dynamics and the third with platelets and the coagulation of blood. Each is in a sense autonomous and yet acts in complementary interplay with the other two.

Phylogenically, the evolution of the intricacies of hemostasis in humans can be traced from the lowest forms of animal life wherein neither vessels nor coagulation are present, through intermediate genera with no mechanism for clotting. It is evident that man is vested with greater assurance against abnormal bleeding; although the sine qua non of his hemostasis is intact vasculature, man possesses compensatory means for partially counteracting deficiencies in this most important structure.

Extravascular Factors

With no other variables, the adequacy of hemostasis is directly related to the quality of perivascular support. Accordingly, severance of vessels of comparable size in different tissues is associated with hemorrhage in proportion to the ease with which the extravasated blood can escape the confines of that particular tissue. Bleeding into solid structures is self-limited, whereas that into loose subcutaneous or submucous tissues may be extensive. Mucocutaneous signs are therefore common in all generalized hemorrhagic disorders.

The clinical characteristics of purpura are also influenced by the efficiency of the tissue macrophages which are respon-

sible for removal of pigments from the breakdown of extravasated erythrocytes; the rate of evolution and regression of ecchymoses and petechiae is thereby governed.

Vascular Factors

The blood vessels involved in purpura are the smallest arterioles (metarterioles), the capillaries and venules. Flow of blood through this system is regulated largely by muscular components found in the metarterioles and the precapillary offshoots. The precapillary vessels dilate suddenly into the capillary loops; at these points the intracapillary pressure is highest and petechial hemorrhages form, irrespective of their causation. Under basal conditions many of the capillaries appear empty, collapsed as a consequence of vasoconstriction. Continued observation with a suitable microscope reveals periodic relaxation of the occluding vessels with a resultant intermittency of flow through their subsidiaries.

The integrity and rhythmic vasomotion characteristic of the basal state may be violently altered by a number of physiologic or pathologic processes. To emphasize the variety of possible influences it is necessary to consider the factors normally operative.

Microcomposition.—Vessels are of mesenchymal origin; those involved in purpura consist in essence of endothelial cells, muscular elements and a supporting matrix. Anatomic integrity is maintained by vitamin C, hyaluronic acid-hyaluronidase ratios, certain hormones and possibly vitamin K, vitamin D and flavonoids. Vitamin C is necessary for the deposition of quality matrix. Hyaluronic acid, a viscous mucopolysaccharide, is a constituent of the matrix; depolymerization by hyaluronidase liquefies hyaluronic acid and thereby impairs the tensile strength of the ground substance. Thyroxin is also required for elaboration of quality matrix. And adrenocortical steroids of the cortisone group decrease capillary fragility through unknown means.

The evidence for vascular effects of the other agents listed is not entirely acceptable. Vitamin K has been shown to counteract the ability of some quinones to induce uterine bleeding of a vascular type in pregnant animals, and may decrease capillary fragility before affecting the prothrombin time in patients with obstructive jaundice. Under experi-

mental conditions, calcium is necessary for the formation of matrix and therefore vitamin D is indirectly implicated; however, no evident clinical counterpart exists. Similarly, although flavonoids have demonstrable hemostatic effects under appropriate experimental conditions, their value in human disease remains unproved.

REFLEX VASOMOTION.—The initial, instantaneous reflection of trauma to a capillary or metarteriolar loop is virtual disappearance of the column of blood contained in the injured vessel. Neurogenic vasoconstriction is responsible. Although momentary, its effect is of sufficient duration to permit a second event to occur.

HUMORAL VASOCONSTRICTION.—Any platelets which may have escaped their vascular confines and others which adhere to damaged endothelium, mass and undergo degenerative metamorphosis thereby liberating a vasoconstrictor substance which bathes the local area of injury. This component has been identified as serotonin (5-hydroxytryptamine), a potent vasoconstrictor present in the circulating blood only in platelets. When the humoral effect is finally dissipated, intravascular mechanisms have become activated; coagulation prohibits further loss of blood.

HUMORAL VASODILATION.—Histamine is an effective vasodilator and thereby capable of counteracting serotonin.

In addition, there must be numerous physiologic factors at present unknown.

INTRAVASCULAR FACTORS

Intravascular factors may be subdivided into two groups, the cellular and the plasma reactants.

CELLULAR REACTANTS.—The platelets are the most important cellular participants in hemostasis. They have numerous functions (Fig. 1). Allusion has already been made to one, namely, their serotonin content and its role in vasoconstriction. In addition, by virtue of their intrinsic adhesiveness platelets are capable of sealing minute leaks in blood vessels by purely physical means; they aggregate to form a white thrombus. A third major category of functions is that concerned with blood coagulation, to be considered in the next section. Lastly, platelets are required for clot retraction. Although the precise significance of clot retraction has not yet been established, most investigators consider that it has,

as its in vivo counterpart, the drawing together of proximate walls of blood vessels which have been severed.

In addition to the function of platelets in hemostasis, there is evidence that both red cells and white cells possess "thromboplastic properties." Plasma which is free of any of the three formed elements is extremely hypocoagulable or, indeed, may be incoagulable. In clinical contradistinction, thromboembolic

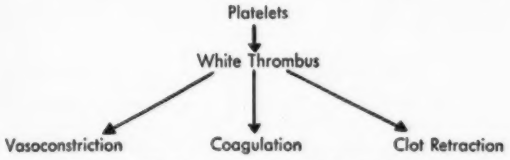

FIG. 1.—Roles of platelets in hemostasis.

disease is relatively common in patients who have an excess of any of the three formed elements.

PLASMA REACTANTS AND BLOOD COAGULATION.—Few subjects in medicine have had more investigation than the coagulation of blood. One consequence has been the acquisition of an elaborate and impressive body of information. But, in addition, the accessibility of blood has led to an endless reduplication of observations. Confusion has often been compounded.

In Figure 2 is presented a concept, synthesized from the data of others, of the present status of our knowledge of blood coagulation. No effort has been made to satisfy the most fastidious or to incorporate pet theories.

The ultimate reaction, the essence of clot formation, is the polymerization of soluble fibrinogen into its insoluble form, fibrin. Thrombin quarterbacks the play, directing not only this key reaction but also assuring its own participation by compelling a number of teammates to arouse its dormant fullback and progenitor, prothrombin. Additional molecules of thrombin are formed from prothrombin. Since the sequence requires the co-operative effort of several factors with the product guiding its own formation, and is catalytic, the term "coautocatalytic reaction" has been employed.

The conversion of prothrombin to thrombin has long been known to require calcium ions and thromboplastin. This classic concept has undergone considerable amplification,

however, on the basis of recent investigations. Two methods of study have been most productive: observations made on isolated coagulation reactants, and on the effects of admixtures of normal and pathologic plasmas. It is now clear that a succession of interactions monitor the production of thrombin from prothrombin. For convenience, they may be divided

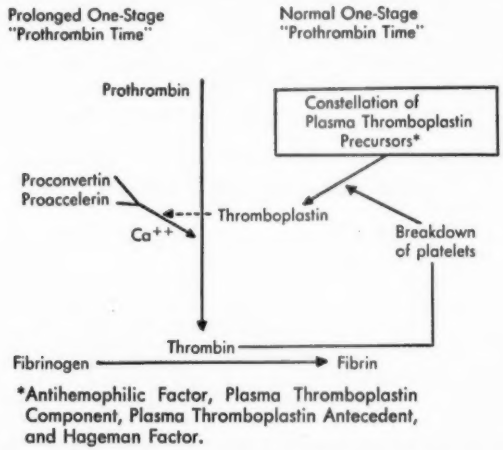

FIG. 2.—Mechanism of blood coagulation. Postulated reactions are divided into those which have no effect on the one-stage prothrombin time and those in which a deficiency is reflected by a prolonged one-stage prothrombin time. The precise interactions are unknown, and information is especially meager concerning the interrelationships of the various precursors of plasma thromboplastin, although platelets are thought to be involved. There is evidence that an accelerator of prothrombin conversion is formed from reactions involving proaccelerin, proconvertin, thromboplastin and calcium.

into first, those which guide the production of plasma thromboplastin (right half of Fig. 2) and, second, those which lead to the formation of serum accelerators of prothrombin conversion (left half of Fig. 2). The sequence of reactions between the constellation of factors concerned with elaboration of thromboplastin is unknown although a series of steps must be involved and platelets are indispen-

sable participants. The serum accelerators have been better identified and therefore it is possible to formulate, tentatively, their mode of interaction. It must be stressed, nonetheless, that final definition is far from realized. Some investigators feel confident that certain reactants in both categories which have herein been assigned specific identities are in fact products of precursors and are not parent molecules. Others propose that in some instances the physiologic effects involve neutralization of anticoagulants and not direct promotion of thrombin formation. The only virtue claimed for the schema presented in Figure 2 is its clinical applicability.

Intravascular coagulation is probably taking place continually at a subclinical rate in health, and is readily apparent at sites of tissue injury. Yet in either instance the process is limited and the autocatalytic reaction discussed above does

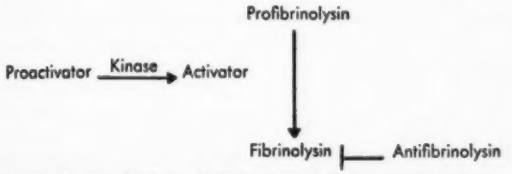

FIG. 3.—Basic mechanism of fibrinolysis. Kinase may be derived from tissue cells or microorganisms such as streptococci (streptokinase).

not proceed at an ever-increasing rate beyond the needs of the organism. Counterbalances are accordingly necessary; these are the physiologic anticoagulants.

There are "broad-spectrum" inhibitors which appear to be capable of blocking numerous reactions; heparin is the prototype for this group. In addition, there are more specific antagonists; the best defined are antithrombin and antithromboplastin. Under pathologic circumstances, these anticoagulants may be increased above normal, or abnormal inhibitors may be produced.

Once formation of a clot is accomplished, means are initiated for its gradual removal. The dissolution is mediated by proteolytic enzymes with affinities for coagulation factors, especially fibrin and fibrinogen. The basic mechanism is presented in Figure 3. In the circulating plasma there is sufficient potential enzyme, if activated, to digest completely in a few moments all the fibrin which could be formed were

all the fibrinogen polymerized. Fortunately, nature has provided inhibitors of proteolysis which normally avert overwhelming activation of the proenzymes.

Stated briefly, coagulation may be activated or inhibited and proteolysis may be activated or inhibited. Both faculties are indispensable. Normal hemostasis is characterized by harmonious interplay of each.

CLINICAL SYNDROMES CAUSED BY DISTURBANCES IN HEMOSTASIS

The clinical disorders induced by various defects in hemostasis are outlined in Table 1. Each will be discussed briefly with the exception of thrombocytopenia, a subject to be considered in detail. Every major category will be introduced by a general statement concerning the clinical manifestations most characteristic for its constituent syndromes, and the most typical pattern of results to be expected on performance of routine tests of hemostatic function. These tests include a platelet count, an examination of a stained blood film for platelet morphology, a determination of bleeding time, capillary fragility, coagulation time in glass and siliconed tubes and clot retraction. Methodology varies in different laboratories, depending on personal preferences and available facilities. The presentation must be brief; for greater detail, the reader is referred to the list of references.

Extravascular Factors

The commonest clinical manifestations of defects in this category are easy bruising and spontaneous formation of ecchymoses; less frequently, hematomas and petechiae are evidenced. Conventional assessments of hemostatic function are generally normal.

Congenital and Familial Forms

Ehlers-Danlos syndrome is a dysplasia of mesenchyme with cardinal features consisting of hyperelasticity of the skin, hyperextensibility of the joints and formation of pseudotumors following trauma. It is transmitted as a dominant gene. Increased friability of the vessels coupled

TABLE 1.—CAUSES OF PURPURA *

Extravascular Factors

Congenital and Familial
1. Ehlers-Danlos syndrome.
2. Hereditary hypoplasia of the mesenchyme.

Acquired
1. Nutritional: cachexia, senile purpura.
2. Metabolic: Cushing's syndrome.

Vascular Factors

Congenital
1. Vascular pseudohemophilia.
2. Hereditary hemorrhagic telangiectasia.

Acquired
1. Traumatic: purpura factitia.
2. Mechanical: orthostatic purpura.
3. Nutritional: scurvy.
4. Infectious: embolic, toxic, purpura fulminans.
5. Neoplastic: tumor emboli.
6. Metabolic: diabetes, uremia, (?) excess circulating histamine, vascular spiders in liver disease, pregnancy, etc.
7. Associated with other vascular disease: hypertension, arteriosclerosis, polyarteritis and hypersensitivity angiitis, other forms of vasculitis, amyloidosis.
8. Immunologic: Schönlein-Henoch purpura, serum sickness, drug sensitivity, associated with autosensitization to erythrocyte stroma.
9. Dysproteinemic: cryoglobulinemia, macroglobulinemia, hyperglobulinemia.
10. Toxic: venoms.
11. Unknown: devil's pinches, purpura simplex.

Intravascular Factors

Platelets
Congenital
Qualitative: hereditary thrombocytasthenia.
Quantitative: thrombocytopathic thrombocytopenia.
Acquired:
Qualitative: acquired thrombocytasthenia.
Quantitative: thrombocytopenia (Table 3).

Coagulation Factors
Congenital or acquired deficiencies of synthesis.
Acquired circulating anticoagulants.
Acquired proteolytic crises: "fibrinolytic purpura."
Acquired intravascular defibrination.

Dermatologic Disorders
Purpura annularis telangiectoides, angioma serpingiosum, Schamberg's progressive pigmentary dermatitis, pigmented purpuric lichenoid dermatitis.

* Those causes of special hematologic interest are concerned with platelet and primary vascular defects, and abnormalities of blood coagulation.

with excessive torsion accounts for the hemorrhagic manifestations.

Hereditary hypoplasia of the mesenchyme, a syndrome of which osteogenesis imperfecta is a variant, is also a constitutional defect, transmitted as a dominant gene. Blood vessels and their framework are involved in addition to the more well-known abnormalities of bone and scleras, and indeed purpura may be the most prominent feature in some instances.

Acquired Forms

Senile purpura is a remarkably common reflection of aging. The skin becomes atrophic and loses its succulence and elasticity. There is a decrease in the subcutaneous tissue as a supportive structure for vessels and its tissue macrophages seemingly become torpid. In consequence are the violaceous subcutaneous extravasations of blood, slow to resolve, seen most prominently on the dorsa of the hands and forearms of elderly persons following minor trauma.

Cachexia per se can result in a similar manifestation, although purpura is generally less frequent and striking than in old age.

Cushing's syndrome is commonly accompanied by easy bruising, most probably due to alteration in extracellular composition. Possibly related is the purpura seen occasionally during administration of adrenocortical steroids, especially of prednisone or prednisolone, even in the absence of other evidences of iatrogenic Cushing's syndrome.

Vascular Factors

Defects in this category are characteristically manifested by either petechiae or ecchymoses and less commonly by hematomas. Prolongation of the bleeding time and a positive test for increased capillary fragility may be noted but are absent in several specific instances as noted below.

Congenital and Familial Forms

Vascular pseudohemophilia is a disorder in which the blood vessels are thought to be inherently incapable of re-

sponse to vasoconstrictor influences. Spontaneous bleeding may occur but the greatest danger lies in even minor accidental or surgical trauma, e.g., tonsillectomy. Hematomas and, rarely, hemarthroses may occur. External blood loss, particularly uterine, may be a prominent complaint. A positive family history is often obtainable and under these circumstances the disorder appears to be transmitted as a dominant. Both sexes are affected. A prolonged bleeding time is the only abnormality found.

Hereditary hemorrhagic telangiectasia is not properly considered a form of purpura, since external blood loss is its most characteristic feature. However, it is included for purposes of completeness. Transmission is as a simple dominant. Pathologically, the basic lesion is a defect in the vessel wall leading to visible dilatation of capillaries and arterioles and in some instances to the development of arteriovenous aneurysms. The typical lesions may assume the appearance of either small violaceous hemangiomas or true spiders. Involvement of both skin and mucous membranes with lesions of various sizes is the rule with, in certain families, the presence also of visceral telangiectasia or even sizable aneurysms in the lungs, liver, spleen and other sites. A more or less stereotyped pattern of distribution and type of lesion is common among members of a family. Iron deficiency anemia is a near-uniform complication, although when the lung is involved secondary polycythemia may be noted. All laboratory assessments of hemostasis are unrevealing.

Acquired Forms

Trauma is the most common cause of acquired purpura. In most instances, the source of injury is readily apparent. However, in occasional cases, usually in women, the trauma is self-inflicted and denied. A most perplexing syndrome can be thereby presented, to be resolved only by repeated sympathetic interviews with the patient. Results of tests of hemostatic function are normal.

Mechanical obstruction to venous return can cause purpura. In its simplest form, this is the basis for the tourniquet test. A similar mechanism obtains when tight garters are worn or when venous pressure is elevated sharply or chronically. Varicose veins, thrombophlebitis, vena caval obstruction

and right-sided heart failure are a few of the many possible etiologic processes. A dramatic example is the purpura seen following paroxysms of coughing in pertussis. Some otherwise normal persons without other evidences of increased capillary fragility will have purpura on their lower extremities on an orthostatic basis. It should be noted, furthermore, that in most patients with underlying generalized hemostatic defects cutaneous manifestations are especially prominent in the legs due to the added factor of a higher orthostatic pressure here than elsewhere. In their pure forms, orthostatic and mechanical purpura are not associated with detectable aberrations in hemostatic function tests.

Nutritional inadequacy can result in purpura if cachexia supervenes. Otherwise, the only clearly established dietary deficiency which is associated with abnormal bleeding on a vascular basis is *scurvy*. Gingival and perifollicular bleeding are characteristic but intramuscular and subperiosteal bleeding are also common, especially in childhood. A rare but interesting complication of protracted therapy with ACTH or cortisone is iatrogenic scurvy. The purpura of ascorbic acid deficiency is associated with a positive tourniquet test and near-total absence of vitamin C in the patient's white blood cells.

Infectious diseases, particularly when associated with a high fever, may induce purpura. Several factors are responsible. Fever alone can increase capillary fragility. In some instances, there may be, in addition, actual lodging of bacteria in capillary loops, e.g., the macules with pale centers featured in meningococcemia. In others, minute thrombi with infarcts are seen, as for example, in rickettsial diseases. Furthermore, emboli may contribute to the picture; the splinter hemorrhages of bacterial endocarditis may be cited. Thrombocytopenia occasionally plays a significant role. Some microorganisms elaborate hyaluronidase which may contribute to the friability of vessels. And, lastly, some infectious agents such as those of epidemic hemorrhagic fever or Weil's disease are extraordinarily damaging to endothelium. But the importance of nonspecific damage to endothelium merits re-emphasis. Studies with injections of pneumococcal polysaccharides into animals have revealed that under appropriate conditions extensive purpura can be induced even though viable organisms are not employed. And clinical corollaries are numerous, e.g., the remarkable degrees of purpura which

may be seen in endocarditis or pneumonia at times when it is extremely difficult to demonstrate bacteremia.

Purpura fulminans is a term applied to severe and usually fatal acute vasculitis with extensive hemorrhage and tissue necrosis occurring during the course of acute infections, e.g., scarlet fever, or the Waterhouse-Friderichsen syndrome. Disturbances of blood coagulation may be associated. The term merely confers special emphasis on the most devastating examples of purpura in infection. It has little diagnostic value and should be discarded.

A positive tourniquet test is commonly but not uniformly observed in purpura with infections.

Neoplastic disease may cause vascular lesions with purpura through either tumor embolism or fibrin embolism secondary to aseptic fibrinous vegetations on heart valves, a phenomenon which may accompany any wasting disease. Routine assessments of hemostasis are unrevealing.

In some *metabolic disorders,* the blood vessels are more fragile than normal. In diabetes, the reasons are unknown. There is only a rough correlation between the presence of purpura and the eyeground findings. A moderately positive tourniquet test is often noted. Uremia is commonly accompanied by abnormal bleeding. A capillary defect is an unproved but postulated mechanism; in addition, recent studies have implicated both platelet and coagulation abnormalities.

Purpura has been attributed, rarely, to an excess of circulating histamine. However, hemorrhagic manifestations are not seen in urticaria alone and it is possible that if purpura is manifested in association with increased histamine levels in the blood other predisposing factors must be operative. Purpura is occasionally noted during menses in girls and women in whom no hemostatic abnormalities can be detected by laboratory assessments.

Bleeding (though not purpura in its true sense) is noted only after trauma in acquired telangiectasia, e.g., in pregnancy or liver disease.

Numerous *systemic vascular disorders* may induce an increase in vascular fragility. Arteriosclerosis is the least likely in itself to account for purpura, since the vessels most involved are larger than metarterioles. With hypertension alone, easy bruising may occasionally be evidenced. But with inflammatory changes as in polyarteritis, hypersensitivity

angiitis and other forms of vasculitis, purpura is sufficiently common to be of diagnostic value.

In amyloidosis, particularly of the "primary" type, easy bruising is a classic feature. Infiltration of vessel walls is the chief etiologic factor. A positive tourniquet test is generally the only abnormal laboratory finding.

Immunologic mechanisms may cause purpura. In serum sickness and drug or chemical sensitivity, petechial or hemorrhagic macular skin lesions may occur. These reactions are often separable from fully developed anaphylactoid purpura, but sometimes boundaries of definition are not precise, and the causes listed in Table 2 may apply to either category.

TABLE 2.—CAUSES OF ANAPHYLACTOID PURPURA *

BACTERIA: Especially Streptococci; also tuberculosis and bacterial vaccines.

DRUGS: Antibiotics (penicillin, streptomycin, sulfonamides, viomycin); antihistaminics; analgesics and antipyretics (aminopyrine, salicylates, acetophenetidin, phenylbutazone; sedatives (barbiturates, chloral hydrate, meprobamate); antiepileptics (hydantoin, phenylethylhydantoin); heavy metals (gold, arsenic, mercury); agents employed in cardiovascular diseases (digitalis, quinidine, mercurials, thiosulfates, ephedrine); agents employed in endocrinologic diseases (estrogens, insulin, thiouracil, carbutamide, tolbutamide); miscellaneous (quinine, menthol, cincophen, dinitrophenol, ipecac).

CHEMICALS: Coal tar derivatives?

FOODS: Wheat, egg, chocolate, milk, beans, tomatoes, potatoes, onions, strawberries, blackberries, plums, nuts, pork, chicken, fish, crab.

PHYSICAL AGENTS: Cold.

OTHER CAUSES: Insect bites, serum sickness.

* The table is merely a guide, since any agent to which history of exposure is elicited must be considered potentially responsible.

Anaphylactoid or Schönlein-Henoch purpura is an acute or chronic generalized angiitis with predilection for cutaneous, joint, gastrointestinal and renal involvement. There is strongly suggestive evidence that the process is due to the development of antibodies directed against the host's own endothelium. It is seen especially often in children or young adults and usually occurs 2 to 3 weeks following a streptococcal infection although, as mentioned, other etiologic factors have also been implicated (Table 2). The characteristic triad consists of purpura, abdominal and joint pains and nephritis. Angioneurotic edema also may be noted. The skin lesions are generally macular or ecchymotic, vary in size and are often confluent. They may be red or violaceous and

though generalized are most prominent on the extremities. The arthralgia may be minimal, or severe and suggestive of acute rheumatic fever. The knees, elbows and fingers are most often involved. Gastrointestinal symptoms vary from minor evanescent cramps to agonizing pain which may closely simulate acute surgical abdominal disorders, particularly acute appendicitis. Melena or hematochezia may be noted. Renal involvement ranges from no detectable abnormality to severe nephritis with gross hematuria and azotemia. Other endothelial surfaces may be involved in the process. Ultimate recovery is the rule but deaths have been reported during the acute stage, and unremitting cases may occasionally evolve into a clinical picture indistinguishable from chronic glomerulonephritis or polyarteritis nodosa.

It should be noted that on many parameters features of anaphylactoid purpura, rheumatic fever and acute glomerulonephritis may overlap.

The test for increased capillary fragility is usually positive.

A few instances have been described, in women only, of tender ecchymoses with surrounding erythema and edema. Autosensitization to erythrocytic stroma has been suspected since either trauma or subcutaneous injections into the patient of a small volume of her own red blood cells has reproduced the lesions. Otherwise, tests of hemostatic function yield normal values.

The *dysproteinemias* associated with purpura are cryoglobulinemia, hyperglobulinemia and macroglobulinemia. The first disorder is featured by a cold precipitable protein in the serum. The second two may be tentatively separated by the "water test," i.e., the prompt appearance of a milky flocculum on addition of a drop of serum to a tube of distilled water if macroglobulins are present. Accurate definition requires ultracentrifugation studies however; an increase in the S-20 component is characteristic of macroglobulinemia. In their idiopathic forms each of the dysproteinemias may be chronic and have a benign course for many years. Hyperglobulinemia and cryoglobulinemia may be secondary to underlying pathology and their courses are thereupon influenced by the primary disease. Multiple myeloma, chronic liver disease, "collagen diseases," lymphomas and chronic granulomas are the commonest underlying diseases. In each instance, any hemorrhagic manifestation due to the dysproteinemia may be modified or aggravated by other factors

such as disturbances of blood coagulation or platelets.

Dysproteinemias per se may be manifested by petechiae, a positive tourniquet test and a prolonged bleeding time, each a reflection of a vascular defect, although its pathogenesis in these syndromes is unknown.

Certain *toxins* regularly induce bleeding from vascular injury. Some snake and scorpion venoms contain endotheliotoxins; constituents more damaging to the patient, e.g., neurotoxins, are generally present also.

Unknown causes for purpura include devil's pinches and purpura simplex. Both are mild and of cosmetic significance only. They are especially common in obese, middle-aged women and consist of circumscribed ecchymotic patches most prominent on the trunk and lower extremities. The two syndromes are probably related if not identical. A family history of similar manifestations may be elicited. These labels are often applied in lieu of accurate diagnosis. Since all assessments of hemostatic function yield normal results, it has been assumed that mild but immeasurable increases in vascular friability are responsible.

Intravascular Factors

PLATELETS

Platelet deficiencies may be either quantitative or qualitative. Their most typical clinical reflections are petechiae and ecchymoses, although menometrorrhagia, gastrointestinal bleeding and hematoma formation may be seen also.

Characteristic abnormalities in assessment of hemostasis consist of a prolonged bleeding time, a positive test for increased capillary fragility, impaired clot retraction and impaired prothrombin conversion, although the clotting time is generally normal.

The functions of platelets are outlined in Figure 1. Single or multiple qualitative defects may occur; thrombocytasthenia is a term employed to designate these disorders. Thrombocytopathia is considered to be a special variety of congenital thrombocytasthenia featured by: (1) uniformly enlarged and bizarre platelets and (2) frequent fluctuations of platelet counts down to thrombocytopenic levels. It should be noted that anisocytosis and poikilocytosis of platelets may occur in some disorders, e.g., following acute blood loss from

any cause, in extramedullary hematopoiesis, and in diseases featured by accelerated platelet production, without any apparent abnormalities in hemostasis; here the terms thrombocytopathia and thrombocytasthenia are not applicable.

Congenital and Familial Disorders

Qualitative abnormalities: Thrombocytasthenia is often difficult to distinguish from vascular pseudohemophilia. Both are featured by easy bruising, bleeding from minor trauma, a prolonged bleeding time and a normal platelet count. A history of similar manifestations in other members of the family may be obtained in either disorder and in these instances transmission appears to be a dominant characteristic. However, platelets are quantitatively and qualitatively normal in the primary vascular disorder whereas, as implied above, a prolonged coagulation time, impaired prothrombin conversion, defective clot retraction and morphologic alterations may be observed with different varieties of thrombocytasthenic processes. The ultimate differentiation between thrombocytasthenia and vascular pseudohemophilia may require observation of the effects of transfusion of viable normal platelets on the hemostatic defects; normal platelets do not correct pseudohemophilic abnormalities.

Quantitative abnormalities: Thrombocytopathic thrombocytopenia is readily diagnosed. In this relatively rare disorder, the platelets are almost the size of erythrocytes and have a more diffuse and fine granulation than normal. Marrow megakaryocytes have similar atypical granulation. And, although intermittent thrombocytopenia is characteristic, the bleeding manifestations occur without relationship to platelet levels because of the basic associated qualitative defects in these cells.

Acquired Disorders

Qualitative abnormalities: Thrombocytasthenia may occur as an acquired disorder which develops de novo or in association with other processes, e.g., uremia and possibly some instances of splenomegaly or leukemia, or following infusion of plasma substitutes. Systematic studies are lacking but it is likely that many presently obscure bleeding tendencies

will ultimately have qualitative platelet defects implicated.

Quantitative abnormalities: Thrombocytopenia is the commonest cause of serious generalized bleeding and its importance in the future will almost certainly be even greater as industrial and military progress results in new means for inducing this old syndrome. Yet many problems remain unsolved. Knowledge of platelet disorders lags several years behind that of diseases of red cells, although the application of known principles of erythrocyte production and destruction has led to rapid advances in knowledge concerning analogous platelet phenomena. Because of the importance of the subject, the major portion of the remaining discussion will relate to thrombocytopenia.

THROMBOCYTOPENIA

The total number of platelets in the circulation remains relatively constant under normal circumstances, as continuous turnover of cell populations replaces older forms with new. Approximately 10 to 15% of the circulating platelet mass is destroyed and replenished each day. Disruption of this equilibrium is reflected in alteration of the platelet count unless compensation is effected. Within limits, an augmented rate of destruction may be counterbalanced by a proportional increment in platelet production. An uncompensated decrease, however, in either platelet viability or rate of formation is manifested as thrombocytopenia, a feature of numerous diseases (Table 3).

The parent cells of platelets are megakaryocytes. With their maturation, cytoplasmic neutrophilia and granularity become evident and in some cells platelet production may be detected. But all mature megakaryocytes do not demonstrate platelet formation and in fact some more basophilic forms may be active while their neutrophilic neighbors appear dormant. The cytoplasm of active cells fragments into fairly uniform spheres 2 to 4 micra in diameter which by unknown devices gain access to the circulation as the disk-shaped, finely granular platelets. With the possible exception of the spleen, no extravascular repository for platelets which have once entered the blood stream is known.

Information is meager concerning the factors which regulate thrombocytopoiesis. Folic acid, vitamin B_{12} and ascorbic acid are clearly required as are basic nutriments. It is pos-

sible that the spleen exerts an inhibitory influence and that adrenocortical steroids may under certain circumstances accelerate formation of platelets. Of great academic interest at present is the autoregulatory mechanism for maintenance of platelet equilibrium. Effective means of repletion of lost numbers are normally operative. An interval of depletion is

TABLE 3.—CAUSES OF THROMBOCYTOPENIA *

Decreased Production of Platelets

1. Replacement of bone marrow: leukemia, carcinoma, sarcoma, lymphoma, granuloma, lipoidosis, sclerosis, fibrosis.
2. Aplasia: due to known causes: chemicals, drugs, radiation, oncolytic agents, idiopathic (Table 4).
3. Deficiency diseases: megaloblastic anemias, scurvy.
4. Some instances of idiopathic thrombocytopenia.
5. Splenomegaly of any cause?
6. Uremia?
7. Viremia, bacteremia (acute phase)?

Increased Destruction of Platelets

1. Splenomegaly.
2. Stagnation of blood flow: extensive hemangioma, congestive heart failure, hypothemia.
3. Thrombotic thrombocytopenia.
4. Incompatible transfusion reactions.
5. Massive blood loss with replacement with bank blood.
6. Autoantibodies for platelets: most instances of idiopathic thrombocytopenia; sensitization to certain drugs (Table 5), associated with certain diseases: lupus erythematosus, some instances of chronic leukemia, some carcinomas, infectious mononucleosis, convalescent phase of acute exanthemata?
7. Accelerated intravascular coagulation: obstetric accidents, amniotic fluid embolism, premature separation of the placenta, eclampsia?
8. Viremia, bacteremia (acute phase).
9. Thrombocytopathic thrombocytopenia.
10. Uremia?
11. Onyalai?

* Note that idiopathic thrombocytopenia is considered in some instances to be due to deficient production and in other instances to accelerated destruction of circulating platelets.

generally followed by hyperplasia of megakaryocytes and overregeneration of platelets. Recent evidence suggests that this regulation according to need is monitored by a circulating thrombocytopoietic factor, presumably protein in nature, but distinct from gamma globulin and fibrinogen.

Causes of thrombocytopenia due to impaired production of platelets are listed in Table 3.

Viability of platelets is readily compromised. Their already

brief life span of 7 to 10 days may be abruptly shortened further because of their remarkable susceptibility to seemingly mild adversity. Platelets embody many metabolic processes, some ubiquitous, some distinct, and although nonnucleated, they have respiratory activity comparable on a volume basis to that of leukocytes. It is debatable whether platelets possess a cell membrane in the usual sense and the distinct possibility exists that some properties attributed to the platelet are not even intrinsic to it. If the speculation is correct, this cell may in some respects be likened to a minute sponge with its contents irregularly influenced by its environment—a gourmet with capricious tastes. A possible consequence of ready access to the metabolic heart of platelets is their rapid destruction by a host of unrelated causes. Viability is extraordinarily vulnerable to storage, contact with foreign surfaces and activation of coagulation. Stasis and injury by immunologic or toxic means swiftly take their toll.

Specific causes for thrombocytopenia due to accelerated destruction of platelets are enumerated in Table 3.

Differential Diagnosis

Thrombocytopenia may be idiopathic or secondary; either variety may be due to impaired thrombocytopoiesis or excessive thrombocytolysis or to a combination of the two processes. Idiopathic forms will be considered separately later. The following is a discussion of secondary varieties.

Secondary Thrombocytopenia

Decreased production of platelets: Most causes within this category require little comment.

Bone marrow replacement will regularly result in a thrombocytopenia unless extramedullary hematopoiesis supervenes. Leukemia is by far the most common etiology. Other causes are listed in Table 3.

Marrow aplasia may be idiopathic or secondary to recognizable agents. In Table 4 are enumerated the causes which are reasonably well documented. Generally, all marrow elements are decreased but occasionally megakaryocytes alone are absent. Therefore, although pancytopenia is the rule, isolated thrombocytopenia may be occasionally noted.

TABLE 4.—EXOGENOUS CAUSES OF BONE MARROW APLASIA

I. *Agents which regularly induce aplasia if exposure is sufficient:*
  1. Therapeutic agents:
    (a) Oncolytic compounds: nitrogen mustard and related compounds, urethane, myleran, antimetabolites (folic acid antagonists, 6-mercaptopurine, etc.).
    (b) Ionizing radiation: roentgen rays, radioisotopes.
  2. Occupational hazards:
    (a) Chemical: benzol, mustard gas.
    (b) Ionizing radiation: roentgen rays, radioisotopes.

II. *Agents occasionally associated with marrow aplasia:*
  1. Therapeutic agents:
    (a) Antimicrobials: arsenobenzols (arsphenamine and its analogues, thiocarbasone, etc.), chloramphenicol, sulfonamides, quinacine, streptomycin*, oxytetracycline?*, chlortetracycline?*, para-aminosalicylic acid?*.
    (b) Anticonvulsants: methylphenylethylhydantoin, methylphenylhydantoin, diphenylhydantoin*, trimethadione, paramethadione, atrolactamide, phenacemide.
    (c) Antithyroid drugs: carbethoxythiomethylglyoxaline*, methylmercaptoimidazole.
    (d) Antihistaminics: pyribenzamine*, phenindamine*.
    (e) Tranquilizers: promazine?*, chlorpromazine?*.
    (f) Analgesics: phenylbutazone*.
    (g) Heavy metals: arsenic, gold, bismuth*, silver*, mercury*.
    (h) Miscellaneous; amphetamine?*, carbutamide*.
  2. Occupational hazards:
    (a) Heavy metals: arsenic, gold, bismuth*, silver*, mercury*, lead*.
    (b) Hair dyes, stove and shoe polishes.
    (c) Insecticides: dichlorodiphenyltrichloroethane*, hexachlorocyclohexane, toxaphene?*, chlordane?*.
    (d) Organic solvents: coal tar solvent naphtha, petroleum naphtha, gasoline*, kerosine* (all four have variable content of benzol), ethylene glycol monomethyl ether, toluene?*, xylene?*, carbon tetrachloride?*.
    (e) Miscellaneous: dinitrophenol, trinitrotoluene, dinitrobenzene, methylisopropylbenzene*.

NOTE: Those agents identified by an asterisk (*) have been rarely incriminated; those followed by a question mark (?) have not been clearly implicated, although the evidence is sufficiently suggestive to warrant their inclusion. Because of the cracking processes employed in petroleum fractionation, it is now difficult to be assured of the relative safety of domestic petroleum as contrasted to coal distillate; benzol may be present in either product. It is also to be anticipated that additional agents currently undergoing clinical trial (e.g., tolbutamide, acetazoleamide, etc.) may ultimately be added to the list.

Megaloblastic anemias are usually accompanied by thrombocytopenia, often pronounced, but seldom sufficiently severe to induce purpura. The platelet count increases as the reticulocyte response to specific therapy takes place. Scurvy is an additional deficiency disease in which a lowered platelet level may be found.

Although not established, it has been suggested from morphologic studies that thrombocytopenia with splenomegaly may be due in part to inhibition of activity of megakaryocytes despite adequacy in their numbers.

Uremia is at times featured by a low platelet count, with or without marrow hypoplasia. Since relative insufficiency of erythropoiesis is operative in uremia it is reasonable to assume that platelet equilibrium may be similarly jeopardized.

Likewise, by analogy to the red cell, it is assumed that the thrombocytopenia of infections during their acute phase may be due in part to impaired thrombocytopoiesis.

Increased destruction of platelets: The life span of platelets is frequently shortened in patients with splenomegaly, presumably due to excessive sequestration of cells in the added mass of splenic tissue.

Closely related, perhaps, are other causes for stagnation of blood flow; extensive hemangiomas in infancy, severe congestive heart failure and hypothermia are examples. As noted earlier, platelets are distressingly intolerant of stasis.

Thrombotic thrombocytopenia is a perplexing disease of unknown etiology, thought to be uniformly fatal, and characterized clinically by hemolytic anemia, thrombocytopenic purpura and migratory transient central nervous system signs and symptoms. Pathologically, the basic lesion is a vasculitis in which are presumably entrapped erythrocytes and platelets; transfused platelets are destroyed almost immediately.

As mentioned above, platelets rapidly lose their viability on storage; this is particularly true with conventional blood-banking methods wherein platelet viability is lost within a few hours. It is not surprising, therefore, that in instances of massive blood loss requiring replacement with large volumes of bank blood, thrombocytopenia rapidly supervenes. In infancy, use of exchange transfusion is an additional example.

Transfusion reactions from incompatible blood induce thrombocytopenia by quite different mechanisms. In part, the fall in platelet count may be due to immunologic incompatibility involving the platelets as well as erythrocytes. In addition, it is likely that platelets are inadvertently entrapped in the red cell sludging that is associated with hemolytic transfusion reactions. And, finally, accelerated intravascular coagulation may be set in motion, with consequent depletion

of platelets. The degree of thrombocytopenia is seldom sufficient to induce bleeding.

Accelerated intravascular coagulation from other causes may be associated with profound thrombocytopenia, although afibrinogenemia is generally the most significant hemostatic defect from the standpoint of therapy. Obstetric accidents are the commonest causes, as will be discussed later.

Viremia and bacteremia have been demonstrated to be capable of inducing acute depletion of circulating platelet numbers. In the older literature, this phenomenon was called "platelet loading." Direct in vivo microscopy has revealed that platelets adhere to one another and to the endothelium when living microorganisms are introduced into the blood stream. At times, the degree of thrombocytopenia must be held at least partially responsible for any hemorrhagic manifestations which may be present.

Uremia is commonly associated with anemia due in part to an accelerated rate of red cell destruction. Although unproved, it is likely that thrombocytopenia in uremia may also have a significant element of accelerated thrombocytolysis in its pathogenesis.

Onyalai is a form of acute thrombocytopenia of unknown etiology observed in Africa and characterized by the presence of hemorrhagic bullae on the mucous membranes. Although its pathogenesis is unknown, the clinical picture suggests that increased destruction of platelets is taking place. The disorder is most common in young adult Bantu men and generally begins with a 1- to 3-day prodromal period of malaise, headache and fever. Although an infectious etiology has been suspected, no causative organism has been demonstrated.

Immunologic mechanisms can induce thrombocytopenia. It has long been known that in a few persons acute "platelet crises" may occur on readministration of certain agents to which they have had previous uneventful exposure. The platelet count in these persons may fall from normal levels to complete absence of cells in 1 to 3 hours, indicating fulminant thrombocytolysis. Recovery generally takes place in 5 to 7 days unless contact with the responsible agent continues, or unless it lingers in the body. Recent evidence has clearly established the immunologic nature of the above clinical sequence. It has been demonstrated that the susceptible person has developed an antibody against his own platelets; apparently certain exogenous (and possible endogenous)

TABLE 5.—EXOGENOUS AGENTS CONSIDERED TO BE RESPONSIBLE FOR CERTAIN INSTANCES OF AUTOIMMUNE THROMBOCYTOPENIA

AGENTS	DEFINITE	PROBABLE	POSSIBLE
Sedatives	Carbamides, allyl-isopropyl-acetyl carbamide (Sedormid®), ethyl-allyl-acetyl carbamide.	Phenylbutazone (Butazolidine®)	Hydantoins: diphenyl hydantoin (Dilantin®), phenylethyl-hydantoin (Nirvanol®)
Analgesics		Paramethadione (Paradione®)	Procaine
Antipyretics	Barbiturates: phenobarbital allyl-isopropyl-barbituric acid (Alurate®), 5-(2 bromoallyl) 1-methyl 5 isopropyl-barbituric acid (Narcodorm®). Pyrazolon derivatives; amino-pyrine (Pyramidon®), phenyldimethyl-isopropyl-pyrazolon. Quinine. Methylparafynol (Dormison®).		Sodium salicylate
Antimicrobials	Sulfonamides: sulfanilamide, sulfathiozole, sulfapyridine, sulfadiazine, sulfamezathine, amino-p-toluene sulfonamide, sulfisoxazole. Arsenobenzols: arsphenamine, neoarsphenamine, sulfarsphenamine, silver arsphenamine, mapharsen, bismarsen. Para-aminosalicylic acid.	Streptomycin Isonicotinic acid hydrazide	Penicillin
Agents employed in cardiovascular diseases	Digitoxin. Quinidine.	Diamox®	Tetraethylammonium chloride
Heavy Metals		Gold	

cular diseases			
Heavy Metals		Gold Silver Bismuth	
Antihistaminics	Chlorprophenpyridamine (Chlortrimeton® maleate) 2-(N-phenyl-N-benzylaminomethyl)-imidazoline (Antazoline®) Diphenhydramine hydrochloride (Benadryl®)		
Agents which influence endocrinologic processes		Iodides Thiourea derivatives: thiouracil, propylthiouracil	Insulin Estrogens Carbutamide Tolbutamide
Foods		Foods: milk, potatoes, wheat, corn, eggs, citrus fruits, anchovies	
Miscellaneous	Dichlorodiphenyltrichloroethane (DDT) Chrysarobin	Tetraethylthiuram disulfide (Antabuse®) Viscum album, mistletoe berries	Leg stocking dye Insect bites Ergot

substances (Table 5) are capable of complexing with platelets. The complex is foreign to the host and is accordingly an antigen, albeit a feeble one, since dissociation of the complex takes place readily. A small percentage of hosts respond to the antigenic stimulus by forming an antibody. The antibody will react only with the complex of platelet and agent. If the responsible agent, usually a drug, is not present, the platelets are unaffected. But only a minute amount of agent (e.g., 0.5 mg. of drug given to a susceptible patient) is required to precipitate acute thrombocytopenia. In the bone marrow, megakaryocytes reflect the impact by a relative decrease in mature forms showing platelet formation. Since all three reactants are required (the platelet, the drug and the antibody in the plasma) and since the body rapidly disposes of most drugs, recovery occurs within a few days, the period needed for megakaryocytes to regenerate platelet-forming cytoplasm and increase their numbers. A rebound thrombocytosis characteristically follows the interval of platelet depletion.

If no further drug is given, the antibody gradually disappears from the patient's plasma over a period of several months only to return again thereafter within a few days if re-exposure takes place.

Proof that the reaction is immunologic is based on (1) its specificity, e.g., if quinine is responsible its optical isomer, quinidine, will be inactive and (2) on the demonstration that complement fixation takes place in the process of platelet lysis. In the absence of complement, only agglutination is observed. An additional important observation has been made—passive transfer of susceptibility. When a normal recipient was given quinine alone, or plasma alone from a patient with quinine-induced thrombocytopenia no change in his platelet count was noted. However, when both were simultaneously administered, fulminant thrombocytopenia developed.

A disorder is designated autoimmune when the host produces antibody against his own tissues. The results of detailed studies of autoimmune thrombocytopenia secondary to sensitization to a few notorious offenders, sedormid, quinine and quinidine led to development of technics which have enabled investigators to incriminate less common causes. Thrombocytopenic patients have been encountered in whom as many as 20 drugs were suspect; in vitro testing for anti-

body has enabled ready detection of the single causative agent. At the present time, numerous agents have thereby been implicated (Table 5).

Autoimmune thrombocytopenia also occurs in association with certain diseases. These will be considered later following discussion of idiopathic thrombocytopenia because the serologic behavior of their antibodies is more akin to that to be described for the idiopathic disorder.

Before leaving the subject of thrombocytopenia secondary to known agents, a word of caution should be introduced. In allergic persons, e.g., patients with hay fever or asthma, exposure to their allergens will induce a transient moderate fall in platelet count, although not to purpuric levels. This should not be taken as evidence for the mechanism described above. It is more likely that the fall in count is related to release of histamine which of itself can bring about decreases in platelet levels.

Idiopathic Thrombocytopenia

Idiopathic thrombocytopenia is a diagnosis made by exclusion and all causes listed in Table 1 must be considered in differential diagnosis. Particular attention should be given to a history of any drug or chemical exposures since recognizable agents, especially those listed in Table 5, can induce a clinical syndrome indistinguishable from the idiopathic disorder. Otherwise, certain features are characteristic of idiopathic thrombocytopenia. The disorder is most common in childhood and in adult women. Except for symptoms referable to blood loss or focal complications, and mild asthenia, the patient feels well; exclusive of the hemorrhagic manifestations (chiefly petechiae and ecchymoses), with any attendant local consequences, he looks well. His vital signs are normal. Nodes, spleen and liver are not palpably enlarged. Hematologic values of the peripheral blood are unremarkable but for thrombocytopenia and normocytic or hypochromic anemia if blood loss has occurred. Marrow aspiration reveals an abundance of megakaryocytes with a preponderance of immature forms and little morphologic evidence of platelet production. Other marrow constituents are intact. L.E. cell preparations are negative. Usual blood chemical determinations and other procedures are unreveal-

ing. When detailed questioning for other etiologic factors is negative and the above findings are present, the diagnosis of idiopathic thrombocytopenia must be listed first in order of preference. In few instances will revision of diagnosis be required and in most of these no means of medical evaluation would have revealed the diagnosis, e.g., miliary granulomas limited to the spleen, subclinical lupus erythematosus with a negative L.E. test or an occult carcinoma not accessible to detection by physical or roentgenologic examination.

The greatest danger is from intracranial hemorrhage, the commonest cause of death in idiopathic thrombocytopenia. With the knowledge at hand that drug thrombocytopenia could be an immunologic disorder, it was logical to investigate next the possibility that immunologic mechanisms were responsible for idiopathic thrombocytopenia. Clinical evidence strongly favored this hypothesis. In many instances, infants born to mothers with the disease were also thrombocytopenic, suggesting placental transfer of some circulating factor. In addition, a small number of instances of concomitant thrombocytopenia and autoimmune acquired hemolytic anemia had been observed. It is not surprising, therefore, that several investigators, working independently and utilizing different approaches, tested the hypothesis that idiopathic thrombocytopenia is an autoimmune disorder.

Almost simultaneously the following observations on patients with idiopathic thrombocytopenia were recorded.

1. Plasma from approximately 70% of adult patients is capable of inducing an abrupt and sustained decrease in the platelet count of normal recipients.

2. Platelets survive only briefly on transfusion into most patients with this disease.

3. Platelet agglutination in vitro may be observed with sera from some patients; it is seldom noted with sera from normal persons.

It was soon realized that each phenomenon could also be observed with patients who had received multiple transfusions. The existence of platelet antigens distinct from those of the erythrocyte was thereby recognized; isoimmunization from inadvertent transfusion of blood containing incompatible platelets had taken place. The similarity of phenomena to those occurring de novo in idiopathic thrombocytopenia was further evidence in favor of the immunologic nature of the latter disorder.

It is now generally accepted that some instances of idiopathic thrombocytopenia are featured by autoantibodies for platelets. Great disagreement exists, however, concerning their incidence. As indicated, plasma from approximately 70% of adult patients contains a thrombocytopenic factor. Normal platelet survival times are seldom observed. Yet in most laboratories sera from only a minority of patients have been found to contain platelet agglutinins. One reason above all accounts for the discrepancy: presently available technics for the serologic study of platelets are inadequate.

The author does not except his own procedure from this generalization. In his own laboratory, however, reproducibility of results has been sufficiently constant and the number of cases studied sufficiently numerous to permit certain formulations.

1. Irrespective of age, sex or duration of disease, approximately three fourths of patients with idiopathic thrombocytopenia have platelet agglutinins in their sera.

2. Responsiveness to therapy is correlated to a considerable extent with the finding of platelet agglutinins; the correlation will be discussed later.

3. Mothers with idiopathic thrombocytopenia and circulating platelet agglutinins will give birth to infants with neonatal thrombocytopenia, whereas those whose sera do not contain agglutinins will have normal infants.

4. So-called primary idiopathic thrombocytopenia of the newborn is due to placental transmission of isoantibodies active against the infant's platelets; the mechanism appears to be analogous to that which obtains for red cell isoimmunization in the pathogenesis of hemolytic disease of the newborn. In both instances the mother is clinically well.

Idiopathic thrombocytopenia without demonstrable platelet agglutinins is a syndrome in which several pathogenic mechanisms are probably operative. Some instances are likely due to circulating autoantibodies which escape detection by present technics. In other cases, an accelerated rate of platelet destruction is present but may be caused by nonimmunologic mechanisms. And, finally, there are patients in whom platelet survival times appear to be normal and a remission may follow administration of plasma from a donor with thrombocytosis; in these persons there appears to be a deficiency of some factor necessary for megakaryocytic maturation, or release of platelets into the circulation.

TABLE 6.—OTHER THROMBOCYTOPENIC STATES FEATURED BY AUTOIMMUNIZATION TO PLATELETS

	NUMBER WITH AUTOAGGLUTININS
Disseminated lupus erythematosus	9 of 11 patients studied (6/6)
Chronic lymphocytic leukemia	2 of 3 patients studied (1/2)
Carcinoma Ovary*, colon* and undetermined primary site*, one instance each; breast two instances	3* of 5 patients studied (1/2)
Selective thrombocytopenia due to drugs. Quinine four instances, quinidine four instances, barbital derivatives and benadryl one instance each	10 patients (0/0)

NOTE: Numbers in parentheses represent number of remissions induced by splenectomy/number splenectomized.

Symptomatic Autoimmune Thrombocytopenia

In patients with certain underlying diseases, autoimmune thrombocytopenia may develop (Table 6). These instances are featured by an adequate number of megakaryocytes in the marrow and lack of demonstrable relationships of the purpura to drug sensitization. Disorders in which this form of thrombocytopenia is most prone to occur are disseminated lupus erythematosus, chronic lymphocytic leukemia and an occasional instance of carcinoma. In the last group, the antibody may be absorbable on the tumor and presumably reflects an immune defense response on the part of the host to his tumor, the thrombocytopenia being due to the chance occurrence of antigenic similarity of platelet antigen to tumor antigen.

In infectious mononucleosis, with or without thrombocytopenia, positive platelet agglutination reactions may be observed. Their significance is questionable, however; perhaps an immunologic phenomenon is responsible but it is also possible that other factors, for example those which cause abnormal results in flocculation tests, or other unknown influences, are capable of producing false positive reactions. In diseases featured by gross distortions of serum proteins and abnormal flocculation tests, e.g., cirrhosis of the liver, reactions considered to be false positives are also common.

Following acute infection, particularly during convalescence from rubella or varicella in childhood, acute thrombocytopenia may develop. There has been speculation that

autoantibodies for platelets or possibly a platelet-virus complex may have developed. The hypothesis is attractive but untested. Only negative results have been obtained when the sera from several of these patients has been set up against normal platelets.

BLOOD COAGULATION

In contradistinction to the clinical manifestations which may occur with vascular and platelet defects, petechiae and hemorrhagic macules are not features of bleeding due to coagulation defects. Instead, hematomas, ecchymoses, hemarthroses and massive external bleeding are most characteristic. It should be stressed, however, that petechiae are helpful only if present; their absence does not exclude vascular or platelet abnormalities.

Laboratory assessments yield results which fall into two gross patterns. The coagulation time performed in a glass tube may or may not be prolonged but in all instances except hypofibrinogenemia, clinically significant defects in coagulation will be reflected by a prolongation of the clotting time when performed in a silicone-coated tube. If the coagulation time in a siliconed tube is prolonged, the results of a one-stage prothrombin time determination* serve to separate the possible disorders into the following two major categories: (1) a normal prothrombin time is presumptive evidence that the coagulation defect resides within reactions outlined on the right half of the schema for coagulation reactions (Fig. 2) and (2) conversely a prolonged prothrombin time suggests an abnormality in reactions diagrammed on the left half. These generalizations obtain because reactions involved in the first category are concerned with the elaboration of an adequate supply of available thromboplastin, whereas those in the second deal with other phases of coagulation. Since an excess of thromboplastin is added as a reagent in the performance of a one-stage prothrombin time deficiencies in the first group are circumvented and the prothrombin time is normal; but inadequacies in the second area are not bypassed, defects are not masked and the prothrombin time is consequently prolonged.

* This procedure is not solely a measure of prothrombin, as will be evident in the subsequent discussion. However, it is the assay procedure employed by most laboratories to which the reader will have access and therefore is used here as a critical means of differential diagnosis.

The further differentiation of disorders of coagulation within each group requires ingenuity in the application of technics which, for the most part, are easily performed. An estimation of the fibrinogen concentration may be helpful. Even more frequently of aid is a study of the effects of addition to the patient's plasma of normal whole plasma, $BaSO_4$-treated plasma or serum; in Table 7 are outlined the characteristics of each. If the prothrombin time of the patient's plasma is normal, observations are made on the effects of the added materials on the coagulation time. If the prothrombin time is prolonged, this procedure serves as the means of evaluation. Appropriate combinations of the unknown with the known plasmas or serum will usually yield a diagnostic pattern of results. Technical details are beyond the scope of this review, but one dictum is generally valid: relatively small additions of normal plasma will correct a coagulation time prolonged due to deficiency of clot-promoting factors, whereas only relatively small proportions of a patient's plasma which contains an excess of clotting inhibitors will prolong the coagulation time of normal plasma. Additional procedures include estimations of rates of prothrombin utilization and thromboplastin generation. Accurate quantitative methods, e.g., two-stage analytical technics for prothrombin and accelerin, are needed for precise measurements.

The following is a brief summary of clinical syndromes. For purposes of general application, division of disorders is into two groups, as before, on the basis of the results of a

TABLE 7.—Characteristics of Normal Plasma, $BaSO_4$-treated Plasma and Serum

	Prothrombin	Proaccelerin	Proconvertin	Fibrinogen	AHF	PTC	PTA	HF
Normal plasma	+	+	+	+	+	+	+	+
$BaSO_4$ plasma	−	+	−	+	+	−	+	+
Serum	−	−	+	−	−	+	+	+

Note: + signs indicate presence and − signs absence of a given factor.

one-stage (Quick) prothrombin time. Statements on relative severity of diseases should be accepted as averages; severity in any given process may vary from subclinical defects to lethal manifestations.

Prolonged Coagulation Time, Normal Prothrombin Time

CONGENITAL AND FAMILIAL DISORDERS.—Various names have been employed to designate the following syndromes. Only a single commonly employed term will be herein used.

Classic hemophilia (antihemophilic factor [AHF] deficiency) is generally thought to be due to a true lack of a clot promoter. However, there are some well-documented observations which suggest that an inhibitor is present which results in an impaired expression of the physiologic effects of the clot promoter. The defect occurs almost exclusively in males and is transmitted as a sex-linked recessive gene by females. But in one third of cases no family history of abnormal bleeding tendency can be elicited. Characteristic are repeated episodes of serious hemorrhage and crippling joint involvement; the patient's life span is usually shortened. Approximately 80% of all patients in the "hemophilia group" have AHF deficiency.

Plasma thromboplastin component (PTC) deficiency is a hemophilioid state with genetic transmission identical to that of classic hemophilia. Its course is generally somewhat less severe. Approximately 15% of all patients with hemophilia and related disorders have PTC deficiency.

Plasma thromboplastin antecedent (PTA) deficiency is a relatively mild form of hemophilioid state thought to be transmitted as a dominant, with both men and women affected.

Hageman factor (HF) deficiency is an asymptomatic disorder, characterized solely by a prolonged coagulation time. Both sexes are affected. Genetic transmission appears to be as a dominant.

In addition to the above instances in which plasma factors are at fault, platelet deficiencies must be included. As indicated earlier, platelets are indispensable participants in the chain of reactions which lead to the production of plasma thromboplastin. Therefore, some instances of congenital

thrombocytasthenia and thrombocytopathia can be associated with a prolonged coagulation time and an impairment of thromboplastin generation.

ACQUIRED FORMS.—Circulating anticoagulants may develop with effects neither directed against thromboplastin nor against the thromboplastin reagent employed in the prothrombin time determination. Under the circumstances, a prolonged coagulation time with a normal one-stage prothrombin time may be encountered. Middle-aged women, patients with disseminated lupus erythematosus and hemophiliacs who have had numerous transfusions of plasma are most prone to develop anticoagulants. But instances have been reported in other diseases and in otherwise normal persons. Most commonly of all, the use of heparin in dosages which have little effect on the one-stage prothrombin time will fulfill the criteria for inclusion in the major category under consideration.

Patients with dysproteinemias may have blood with a prolonged coagulation time and a normal prothrombin time. In some, this may be due to the physical properties of sera containing a nonoptimal concentration of colloid for coagulation reactions. In others with liver disease, there are multiple defects among which impairment of reactions depicted on the right half of Figure 2 has been postulated.

Acquired thrombocytasthenias and thrombocytopenias merit the same comments as given for the congenital and familial varieties.

Prolonged Coagulation Time, Prolonged Prothrombin Time

CONGENITAL AND FAMILIAL DISORDERS.—(1) Hypoprothrombinemia, (2) hypoproaccelerinemia, (3) hypoproconvertinemia. These three congenital deficiencies are rare and thought to be transmitted as dominant genes. The first is a true prothrombin deficiency; the last two cause spurious prolongations of the one-stage prothrombin time.

Hypofibrinogenemia probably has a hereditary pattern of transmission but studies are too few to be certain of its nature. Because of the decrease or absence of fibrinogen a clot forms slowly or not at all on performance of the prothrombin time, and therefore the resultant value is spuriously long.

ACQUIRED DISORDERS.—Hypoprothrombinemia may be due to (1) failure of synthesis secondary to vitamin K deficiency, e.g., from failure of absorption of the fat-soluble vitamin as may occur in sprue, or obstructive jaundice or from deficient stores in hemorrhagic disease of the newborn, (2) competition with Vitamin K from Dicumarol* or related drugs, (3) inability of synthesis because of liver damage or (4) excessive rate of utilization as is found in accelerated intravascular coagulation, e.g., in acute intravascular defibrination in obstetric accidents.

Hypoproconvertinemia reflects the same processes as listed for hypoprothrombinemia.

Hypoproaccelerinemia may be due to liver injury or excessive utilization. Vitamin K is not necessary for production of proaccelerin.

TABLE 8.—CAUSES OF ACQUIRED AFIBRINOGENEMIA

Fibrinolysis*
Severe trauma
Shock
Transfusion reactions
Burns
Obstetric accidents (see below)
Carcinomatosis—especially prostatic
Cirrhosis of the liver
Acute leukemia
Defibrination
Obstetric accidents: premature separation of the placenta, amniotic fluid embolism, eclampsia?, intrauterine fetal death

* Fibrinolysis is often superimposed on late stages of defibrination.

Hypofibrinogenemia may be due to failure of production because of massive hepatic necrosis but is more commonly caused by either excessive rate of utilization or intravascular fibrinolysis. Intravascular defibrination is thought to be due to introduction into the circulation of thromboplastic substances. Activation of fibrinolysis is poorly understood but it is known that mitochondria and microsomes of cells are rich in an activating kinase, and presumably may serve as the source of the activators. In many disorders the processes of defibrination and fibrinolysis are superimposed. The causes for hypofibrinogenemia are listed in Table 8.

It should be noted that in instances of accelerated intravascular coagulation or fibrinolysis the coagulation time

tends to be shorter than normal until a fibrinogen level below 50 mg. % develops.

PURPURAS OF COMPLEX ETIOLOGY

As has been intimated, some purpuras are associated with multiple defects in hemostasis. Included are purpuras of uremia, the parenchymal liver diseases, the dysproteinemias, obstetric accidents and following administration of plasma substitutes. But no mention has been made of bleeding in patients with polycythemia or thrombocythemia; in these persons, several abnormalities may contribute to the purpura. A high platelet count per se is often associated with purpura, although the reason is not clear. Microinfarcts may be a factor. A lowered fibrinogen level may be found and in polycythemic states, since there is relatively less plasma per unit volume of whole blood, any deficiencies of plasma reactants would assume even greater significance.

The succulence of the tissues due to an expanded blood volume probably plays a role in polycythemia. Clinical discrepancies may be startling; a patient may have simultaneous evidence of intravascular thromboses and easy bleeding from minor insults.

THERAPY

Management of the purpuras may be divided into the following categories:

1. Therapy of underlying diseases and precipitating causes.
2. Transfusions of whole blood for replacement of blood loss.
3. Local measures: cauterants, packing and pressure dressings.
4. Specific measures: vitamins C and K, adrenocortical steroids, splenectomy, platelet transfusions, transfusions of fresh plasma, infusions of fibrinogen and injection of protamine sulfate.

Categories 1 and 2 will not be discussed, since their application is self-evident. Under category 3 only one comment is warranted: if the symptom is chronic and recurrent, e.g., epistaxis in hereditary hemorrhagic telangiectasia, caution

should be exercised in the use of cauterants since their repeated usage may lead to irreversible tissue injury.

It will be noted that under category 4 no mention is made of use of calcium or flavonoids. There is no clinical bleeding disorder in which calcium has merit. This cation is present in excess as relates to coagulation, and tetany or cardiac death would supervene before hemorrhage from hypocalcemia could develop. Flavonoids, despite their effects under certain experimental conditions, have not been shown to have clearly established effects in human disease. Also, the use of estrogens has not been listed, since their evaluation is only now being conducted and convincing proof of their value has not yet been set forth.

Vitamin C is of value only in ascorbic acid deficiency.

Vitamin K is effective in bleeding due to inadequate absorption of fat-soluble vitamins, or deficiency conditioned by Dicumarol® antagonism. In the first instance, water-soluble synthetic preparations are suitable; a dosage of 10 mg. daily is adequate. But to overcome Dicumarol® effects, vitamin K_1 must be employed. Within a period of several hours, the prothrombin time will return toward normal. A preparation of K_1 emulsion is available in 50 mg. ampules for intravenous administration; dosage will vary, depending on the degree of hypoprothrombinemia, the amount of Dicumarol® given immediately preceding the bleeding episode and the need for continued anticoagulation. With larger doses of vitamin K_1, e.g., over 50 mg., anticoagulation cannot be reinstated with Dicumarol® for several days because of the potency of this material in counteracting the effects of Dicumarol®.

Transfusions of fresh plasma are indicated in any of the coagulation defects caused by lack of clot-promoting factors, but most particularly in hemophilia and related disorders. Stability of clotting factors varies and therefore some are present in only low concentration in plasma obtained from blood which has been stored in a bank for several days. Antihemophilic factor and proaccelerin are storage-labile unless the plasma is freshly frozen or lyophilized, and fibrinogen also deteriorates, but less rapidly. The other factors are relatively more stable. Therefore, for example, fresh plasma is indicated in AHF deficiency, whereas plasma stored several days is still useful in PTC deficiency. Dosages depend on circumstances. Ordinarily 250 ml. of plasma every 4 hours is adequate but in episodes of dangerous bleeding, e.g., head

injury or emergency surgery, an exchange transfusion of 2 to 4 liters or more of fresh whole blood may be needed.

Concentrated fibrinogen is also of value; it is indispensable in the management of the afibrinogenemias. The material is expensive and also often contains the virus of serum hepatitis. Therefore, valid indications must be present to warrant the use of concentrated fibrinogen. In acute afibrinogenemia, 5 Gm. should be administered immediately and repeated as frequently as needed.

Protamine sulfate rapidly counteracts the effects of heparin and is accordingly useful when bleeding is caused by administered heparin or the rare instances of spontaneous hyperheparinemia. A dosage of 25 mg. given intravenously will immediately counteract the effects of heparin in the average patient.

Search for exposure to exogenous agents which may have been responsible for the development of purpura is mandatory in the proper clinical settings. It is of particular importance in anaphylactoid and thrombocytopenic purpura; the recognized causes are listed in Tables 2, 4 and 5. When a relationship to a given exposure seems possible, purpura should be treated primarily by removal from contact with the suspected agent. In instances of bacterial causation, appropriate antibiotic regimens should be employed. Work-up for an allergic basis with skin tests or similar procedures and in thrombocytopenia with serologic technics may reveal the offending agent. It must be admitted, however, that in the author's experience these approaches have been of only occasional value. Nevertheless, they are required whenever careful questioning gives rise to suspicion. The most dramatic responses to removal of suspected agents have been seen in instances of autoimmune thrombocytopenia due to drugs.

More detailed discussion will be given to the use of adrenocortical steroids, splenectomy and platelet transfusions. First, general comments on the three measures will be presented, then specific application of each therapeutic approach will be considered.

General Comments on the Use of Steroids, Splenectomy and Transfusions of Platelets

1. *Adrenocortical steroids:* ACTH, cortisone, hydrocortisone, prednisone and prednisolone produce similar hemato-

logic effects. The following desirable responses are possible:

(a) An improvement in capillary fragility may be observed independent of an increase in platelet level.

(b) Elaboration of platelet antibodies may be inhibited.

(c) Rate of formation of platelets may be enhanced.

Evidence for the first two effects is substantial, whereas for the third role only suggestive data have been obtained: thrombocytopenia which has been attributed to impaired thrombocytopoiesis has in isolated instances appeared to respond to large quantities of steroids.

Prednisone and prednisolone are currently most popular because of their more limited capacity for inducing sodium retention. The improvement in capillary fragility may be evident within several hours; the other effects generally require several days, if they occur at all in any given instance.

2. *Splenectomy:* Splenectomy is a procedure with merit for the following reasons:

(a) The spleen is the site most capable of removing damaged though physiologically useful platelets from the circulation.

(b) The spleen produces platelet antibodies; this is a role of secondary importance.

(c) The spleen may inhibit proliferation of megakaryocytes or their ultimate cytoplasmic fragmentation into platelets. This concept, although speculative, has been advanced because of morphologic evidences of increased platelet production following splenectomy and also because splenic inhibition of erythropoiesis has been clearly demonstrated in some instances of anemia.

In instances of favorable response, bleeding promptly ceases and the platelet count usually increases within a few hours or, at the latest, within a few days.

The risks of splenectomy are often overemphasized. Surgical casualties in past years are frequently included in current appraisals. Present-day mortality is low, however; in the experience to be cited there have been no deaths during the procedure and in only one instance, a patient who expired with hepatic necrosis a few days postoperatively, did surgical intervention seemingly contribute to a fatality.

An increased incidence of serious infections, e.g., meningitis, as a remote consequence of splenectomy in children has been suspected. Hematologists whose practice is chiefly limited to adults do not generally believe that there is a

greater number of remote infections in their splenectomized population.

3. *Platelet transfusions:* Platelet viability is vulnerable to storage of blood for even a few hours. Ethylene diamine tetra-acetic acid, disodium salt, is the best anticoagulant, or direct transfusions with nonwettable equipment, i.e., siliconed syringes, may be employed. Under optimal conditions, the transfused platelets survive for only a week but a formidable variety of adversities can shorten the time to a negligible value. Minor breaks in technic of venesection in the donor can activate coagulation, thereby damaging platelets, or in technic of transfusion can lead to local deposition of a sizable portion of the administered platelets. Splenomegaly usually results in a shortened cell life span. Platelet isoantibodies or autoantibodies in the recipient's plasma cause rapid breakdown of these elements.

Even more discouraging is the prospect that even if optimal transfusions are accomplished subsequent platelet survival times in the recipient will, with great regularity, become progressively shorter. Isoimmunity develops and since the clinically important platelet antigens do not correspond to those in the erythrocyte, suitable grouping sera which would permit selection of platelet-compatible donors are not available.

Accordingly, at present, transfusions of viable platelets have real value only when conditions for platelet survival are satisfactory and the anticipated need for this therapy does not exceed a few weeks in duration.

Because of the difficulties in achieving significant long-term aid from transfusions of viable platelets, substitute approaches have been attempted. Nonviable platelet concentrates and extracts from platelets and other tissues have been used. These approaches are still under evaluation.

Although the term "platelet transfusion" is appealing because of its implication as replacement therapy and a panacea for all varieties of thrombocytopenia, the procedure has extremely limited application. The manifestations of thrombocytopenia can often be controlled by steroids, thereby decreasing the need. In addition, the indiscriminate use of platelet transfusions leads to isoimmunization in advance of the time when replacement therapy might be most useful.

Specific Clinical Uses of Steroids, Splenectomy and Transfusions of Platelets

Adrenocortical steroids are the only available "broad spectrum" treatment for purpura; used in moderation, they may have beneficial effects on increased vascular fragility in a variety of disorders. But they also can induce iatrogenic Cushing's syndrome and iatrogenic scurvy. Numerous other contraindications to their employment must be considered. With the exception of many causes of thrombocytopenia and some instances of anaphylactoid purpura, relief of bleeding manifestations by cortisone and its derivations is only partial and unpredictable; it is therefore unwise to administer these agents over a long period without clear indications. But they may be employed as a supplemental measure in acute exacerbations of bleeding.

1. *Anaphylactoid purpura:* In anaphylactoid purpura, remissions coincident with the administration of steroids have been described. But in the author's experience most patients have not been significantly benefited and the benevolence of nature and time have appeared more often to be of value. Yet the acute phase is attended with a significant though small mortality and the chronic disorder is not always readily separable from other forms of vasculitis. Therefore, the measures available should be given a trial.

2. *Thrombocytopenic purpura:* All three measures—steroids, splenectomy and transfusions of platelets—have application in thrombocytopenia.

The last has the least usefulness, as has been indicated. But in acute transitory thrombocytopenia due to irradiation, chemicals or drugs, platelet transfusions may be lifesaving in a few instances and minimize the hazards in many additional cases. The ideal candidate is a patient who has never been transfused, does not have splenomegaly, and in whom the projected duration of thrombocytopenia from the time of institution of platelet transfusions is only 4 to 6 weeks. In the author's opinion, platelet transfusions are virtually useless in cases of autoimmune idiopathic thrombocytopenia.

Beyond treatment of underlying diseases, therefore, the choice of regimen generally lies between splenectomy and use of steroids. Consideration of these two measures in the management of idiopathic thrombocytopenia will serve as a

framework for their application to treatment of the secondary disorders.

(a) *Idiopathic thrombocytopenia:* Before the advent of steroidal therapy, splenectomy was the sole clearly useful measure for the management of idiopathic thrombocytopenia but in the past few years the merits of hormonal management have been demonstrated. In the selection of therapeutic regimens, both clinical and physiologic criteria are now employed. Some regard the age of the patient plus the severity and the duration of his disease as the sole determining factors; the author believes that the presence or absence of agglutinins for platelets in the serum is an additional and valuable guide.

There is general agreement that, in children, thrombocytopenia is better tolerated and spontaneous recovery more frequent than in the older age group. Therefore, pediatric hematologists hesitate to recommend splenectomy, and if the recent evidence for an increased incidence of remote infections in splenectomized children can be confirmed there should be even greater reluctance to have splenectomy done in childhood. Accordingly, therapy with steroids is generally considered to be the treatment of choice for this age group. However, if purpura persists beyond 6 months, splenectomy is commonly recommended. It seems reasonable to conclude that in childhood splenectomy for idiopathic thrombocytopenia is a procedure of second choice, to be employed early in the disease only in extreme circumstances or if steroids are contraindicated.

Some hematologists now teach that in adults also splenectomy is an obsolete procedure; to these men, selection of a therapeutic regimen is therefore simple and steroids are given. However, most investigators still feel compelled to discriminate between the candidates most appropriate for surgical and those best suited to medical therapy.

Some propose as a clinical guide that the disease be divided into acute and chronic forms. Acute cases are treated medically, and splenectomy, when done at all, is reserved for chronic cases. Presumably the latter will ultimately require splenectomy because of self-perpetuating mechanisms which would induce relapse if steroids were discontinued even though remission accompanied their administration. But the clinical subdivision is usually not readily made since most patients have acute thrombocytopenia when first seen by

their physicians and prediction of its ultimate duration is not possible, although most instances in adults, if untreated, run a chronic or relapsing course.

Accordingly, other means of selection are desirable, and to this end an attempt at physiologic classification has been made. Idiopathic thrombocytopenia has been subdivided into *immunologic* and *nonimmunologic* varieties on the basis of presence or absence of agglutinins for platelets in the patient's serum (Tables 9 and 10). The percentage of cases

TABLE 9.—PLATELET AGGLUTININS DEMONSTRATED

Incidence:	
153 of 201 patients	76%
Response to splenectomy:	
72 of 84 patients	83%

TABLE 10.—PLATELET AGGLUTININS NOT DEMONSTRATED

Incidence:	
48 of 201 patients	24%
Response to splenectomy:	
5 of 23 patients	22%

included in the two categories varies greatly in different laboratories because serologic studies of the platelet are in their infancy. The author, therefore, cannot compare his own experience with that of others. In three fourths of his patients, platelet agglutinins have been demonstrated. Neither age nor sex nor duration of the patient's disease have influenced the percentage of positive results obtained. But, as indicated in Tables 9 and 10, there is an apparent correlation between the presence or absence of agglutinins and the patient's response to splenectomy. Whereas 4 out of 5 patients with demonstrable agglutinins in their sera respond to surgery, only one fifth of those without antibody for platelets are similarly benefited. It would appear, therefore, that an additional criterion may be employed for the selection of candidates for splenectomy. But general agreement on this matter will not be achieved until the technic for demonstrating platelet agglutinins can be simplified, standardized and made more precise.

The author believes that both clinical appraisal and serologic results should be utilized. The following is the formulation employed:

1. If mucocutaneous and other bleeding is severe, splenectomy is carried out immediately. Similarly, intracranial bleeding irrespective of other manifestations is considered indication for emergency surgery. Admittedly, the most meticulous observation has limitations, sudden and fatal bleeding may take place in patients who have mild or minimal overt manifestations of their thrombocytopenia while other persons with more profound signs may have no serious consequences even over a period of several years. Nevertheless, a reasonably useful correlation exists between the clinical picture and the dangers at the moment.

2. If purpura is less pronounced, steroids are administered and studies for platelet agglutinins are undertaken. The initial dose of prednisone is 50 to 100 mg. daily.

(a) If platelet agglutinins are demonstrable and no platelet response to steroids has occurred after 1 week, the dosage is doubled or tripled for an additional week. If thrombocytopenia persists, splenectomy is then performed. But if the platelet level has increased, medical therapy is continued until a normal count has been achieved, whereupon steroids are gradually discontinued; if relapse follows, splenectomy is carried out. Alternatively, if only a small maintenance dose of steroids is required to perpetuate remission, splenectomy may be deferred, depending on the patient's proximity to a competent surgical service should emergency operation be required and on his economic status. The cost of protracted medical therapy is greater than that of surgery in most instances, especially when coupled with the fact that in the experience herein cited, splenectomy has been ultimately warranted in most adults. The use of steroids, furthermore, is not without its inherent dangers.

(b) If no platelet agglutinins are demonstrable and no response to steroids is evident even on increased dosage, the regimen is nevertheless continued, since subjects in this group are less responsive to splenectomy. However, surgery is ultimately warranted in many instances because of failure of response to medical therapy, complications from steroids or the need for a prohibitively high dosage to sustain a remission.

If dangerous bleeding manifestations supervene at any time during medical therapy, emergency surgery may be recommended.

It should be reasserted that all criteria are fallible in a

significant number of patients. Approximately 5% of persons are in no sense benefited by any combination of currently available measures, another 20% receive only incomplete though variable degrees of improvement, and of the 75% in whom lasting remissions are achieved, one quarter would have experienced spontaneous recovery. Accurate analysis of relative effects of therapy is therefore not possible, but it is estimated that splenectomy has been of lasting value to patients at least twice as frequently as has the use of steroids.

Assays for platelet agglutinins are not generally available. In their absence, choice of candidates for splenectomy should be guided by (1) the clinical criteria presented for the initial selection of emergency surgery versus medical therapy and (2) the adequacy of the responsiveness of the purpura and thrombocytopenia to steroids over a 2- to 3-week period. It is the author's conviction that the greatest danger to the patient resides in the complacency of his physician; protracted trial with regimens which have failed to induce remission is to be decried irrespective of the number of criteria at hand for their selection.

(b) *Idiopathic thrombocytopenia in pregnancy and in the newborn:* Idiopathic thrombocytopenia in pregnant women may or may not be associated with autoantibodies for platelets. In the infant, idiopathic thrombocytopenia may be due to placental transfer of maternal antoantibodies (i.e., reflecting disease in the mother), or of isoantibodies (the so-called primary idiopathic thrombocytopenia of the newborn, analogous to hemolytic disease of the newborn, and unaccompanied by evidences of maternal thrombocytopenia).

In general, management of the maternal disorder is as outlined for nonpregnant patients but may be modified by two considerations:

1. If the woman has autoimmune idiopathic thrombocytopenia, her infant will almost invariably be affected (Table 11). Similarly, if she had autoimmune purpura relieved by

TABLE 11.—AUTOIMMUNIZATION TO PLATELETS

Number of mothers with thrombocytopenia	15*
Number of infants born to these mothers	26
Number with neonatal thrombocytopenia	25
Number without neonatal thrombocytopenia	1**

* Eight splenectomized previously; five in complete remission, two in partial remission, one in relapse. Seven thrombocytopenic and not splenectomized.

** Said to appear normal; no hematologic studies performed.

splenectomy, the same correlation often obtains because of the frequent persistence of antibody, despite clinical remission following splenectomy. In contrast, if the mother has nonimmunologic thrombocytopenic purpura, her baby's platelet level will be normal (Table 12).

TABLE 12.—No Autoimmunization to Platelets

Number of mothers with thrombocytopenia	6
Number of infants born to these mothers	6
Number with neonatal thrombocytopenia	0
Number without neonatal thrombocytopenia	6

2. Either steroids or surgery might endanger the fetus early in pregnancy; the first may induce congenital anomalies, the second may precipitate abortion. The likelihood of adverse effects on the fetus from either measure diminishes later in pregnancy.

Accordingly, an effort is made to avoid the use of steroids during the first trimester of pregnancy and then to maintain the mother on these agents later until a viable infant may be expected. Thereupon, if platelet antibodies were present initially, but a normal platelet level has been now achieved, the patient should be allowed to deliver normally. If still thrombocytopenic, although free of purpura, she should receive an increased dosage of steroids in an effort to inhibit further antibody production and thereby protect the infant. But if thrombocytopenia and purpura persist, splenectomy and cesarean section may be undertaken. Lastly, in the patient previously splenectomized for autoimmune thrombocytopenia and now in remission, if agglutinins are still demonstrable, steroids may nevertheless be given to the mother to decrease elaboration of antibody which might gain access to the infant's circulation.

If platelet antibodies have not been demonstrated, splenectomy should be performed only if hemorrhagic manifestations are pronounced despite steroidal therapy since, for reasons unknown, remission may occur following delivery.

In no instance herein cited has there occurred either a death or residual damage in the mother from the coexistence of thrombocytopenia and pregnancy.

Infants recover spontaneously from neonatal thrombocytopenia over a period of 1-2 weeks to 4-5 months. The time of greatest danger is the period of actual birth and the few days

immediately thereafter. The most important measure from the infant's standpoint, therefore, is anticipation of the disorder, thereby taking precautions to minimize birth trauma; the prognosis otherwise in the infant is good and may be improved with steroids. It is possible to predict the development of neonatal thrombocytopenia in infants born to mothers with autoimmune thrombocytopenia, but in the absence of a history of previous episodes, the isoimmune form of thrombocytopenia in the newborn (Table 13) cannot be anticipated.

TABLE 13.—ISOIMMUNIZATION TO PLATELETS

Number of mothers (all clinically normal)	6
Number of infants born to these mothers	7
Number with neonatal thrombocytopenia	7
Number without neonatal thrombocytopenia	0

If foreseen, some of the dangers of neonatal purpura may be averted by special care on the part of the obstetrician. Of particular importance is avoidance of instrumentation in delivery and ability and willingness to perform a delivery by section should it appear warranted. There have been no deaths or residual effects in the experience with infants presented in Tables 11 and 13 when awareness of the dangers was known to the obstetrician. But 4 neonatal deaths occurred in 9 deliveries performed without forewarning.

(c) *Secondary thrombocytopenia:* Steroids have benefit on the capillary defect, as in idiopathic thrombocytopenia and therefore are widely employed. In addition, they may favorably alter the underlying disease as in lupus erythematosus and thereby improve the platelet level. But in the present experience if the bone marrow has been cellular with respect to megakaryocytes, a drug or chemical causation has been excluded, and the prognosis is otherwise reasonably good, criteria similar to those for idiopathic thrombocytopenia have been cautiously applied for selection of candidates for splenectomy. The greater number of variables has often influenced and led to deferral of the ultimate decision. Positive platelet agglutination reactions, presumably spurious, are common in sera of patients with distortions of their serum protein profiles. Contraindications to splenectomy are more common in secondary thrombocytopenia. The over-all responsiveness to therapy is understandably less in secondary

thrombocytopenia and the ultimate prognosis more unpredictable than in patients whose purpura is of the idiopathic variety.

SUMMARY

Purpura is a physical sign featured in a variety of unrelated illnesses, the ultimate reflection of a number of derangements of hemostasis. An attempt has been made herein to present a clinically applicable schema for the physiologic approach to differential diagnosis and treatment of the ubiquitous manifestation.

Normal hemostatic mechanisms are subdivided anatomically into extravascular, vascular and intravascular components. It is stressed, however, that each acts in complementary interplay with the other two. The known participants in each category are briefly discussed.

Clinical syndromes are enumerated and their pathogenesis and manifestations considered. An attempt is made to present general features of each group of related hemorrhagic disorders and to list the cardinal features of each of its members.

Therapeutic measures are discussed first in general terms and then with specific reference to the various disorders of hemostasis. Greatest attention is given to thrombocytopenic purpura. Idiopathic thrombocytopenia is divided into immunologic and nonimmunologic varieties on the basis of results of serum assays for platelet agglutinins, and the greater responsiveness to splenectomy of patients with antibodies (83%) as compared to those without agglutinins (22%) is stressed.

A plea is made to avoid the indiscriminate use of any agents claimed to have a role in normal hemostasis or any influence on defective hemostasis in lieu of accurate diagnosis and thoughtful appraisal.

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removal of the cause. If this is impossible, blockade of the goitrogenic influence may be successful if iodine or thyroid hormone is given. In those patients whose goiters are so large that they present a mechanical problem, or when the possibility of carcinoma is likely, surgery may be advisable.

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